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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,369	12/26/2006	Philippe Dupraz	ARS.126	2134

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EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
09/29/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slepatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/573,369	DUPRAZ ET AL.	
	Examiner	Art Unit	
	MARIA MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-48,50,52,54-56 and 59-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *50,52,60 and 61* is/are allowed.

6)☒ Claim(s) *45-48 and 54-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/20/10 has been entered. Claims 45-48, 50, 52, 54-56 and 59-64 are pending. Claims 63 and 64 are eligible for rejoinder expect the claims read on production of a polypeptide of interest whereas the base claims do not include a polypeptide of interest and therefore the claims are not commensurate in scope with the allowable claims.

Claim Objections

Claims 45, 48 and 59 are objected to because of the following informalities: claim 45 has been amended to recite "and a polypeptide of interest" which appears to mean that the polypeptide of interest is fused to the IgSP-tPA pre-propeptide. For clarification, the claim should be amended to recite ----fused to a polypeptide of interest--.

Claim 48 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 48 is outside of the scope of claim 45 as claim 45 is limited to a sequence whose C-terminal end is Arg-Phe-Arg-Arg.

Applicant is advised that should claim 55 be found allowable, claim 59 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 55 and clam 59 are duplicates.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 45-48 and 54-59 under 35 U.S.C. 103(a) as being unpatentable over Ashkenazi et al (WO9953059; see entire document) in view of Patel et al (WO0052158; see entire document). **This rejection is maintained for reasons of record in the office action mailed 9/25/09 and restated below.**

Applicants claim a DNA construct comprising SEQ ID NO:3, mouse IgSP operably linked to tPA consisting of amino acids 23-32 of SEQ ID NO2 and fused to a polypeptide of interest. .

Ashkenazi et al teach a construct comprising a human tissue plasminogen activator signal sequence fused to an IgG 1 sequence (see figure 1 and brief description). The tPA molecule is

provided in SEQ ID NO: 4 and 7 of Ashkenazi et al and consists of either amino acids 22-32 or amino acids 23-35 of SEQ ID NO:2. The occurrence of an extra amino acid in SEQ ID NO4 is demonstrated as not necessary by deletion in SEQ ID NO:7 (page 12). Furthermore the sequence can comprise TNFR sequences (a polypeptide of interest). The constructs are grown in CHO cells (page 15). Ashkenazi et al do not teach that the signal sequence is SEQ ID NO:3.

> FIG. 1. Diagram of a tumor necrosis factor immunoglobulin chimeric molecule (TNFR-IgG1) and signal sequences. TNFR-IgG1 is a chimeric protein consisting of the extracellular domain of the p55 TNF receptor fused to the hinge and Fc domain of an immunoglobulin heavy chain. TNFR-IgG1 is secreted as a homodimer with four N-linked glycosylation sites (squares) per monomer. **The proteins expressed in this study were synthesized using the wild type TNFR signal sequence containing 29 amino acids (SEQ ID NO: 2), or a combination of the TNFR signal sequence and the signal and/or pro-sequence of human tissue plasminogen activator (tPA) (SEQ ID NO: 1).**

> (page 6) "Pre -pro" or "signal -pro" peptide as used in the context of the present invention is meant to refer to an amino acid sequence such as that naturally associated with a mammalian t-PA which acts to direct the secretion of a mature polypeptide, for example, a mammalian t-PA, from a cell. As used herein, the term "signal -pro peptide" includes the "pre-" or "signal" sequence such as that naturally associated with a mammalian t-PA which functions to bind to the signal-recognition particle and direct the protein to the lumen of the endoplasmic reticulum (ER).). **A "signal" sequence is an amino acid sequence, characteristically hydrophobic in nature, cleaved by signal peptidases in the ER. For example, the signal sequence of t-PA is generally removed from the nascent t-PA co-translationally.**
>
> **(page 12) For example, N- or C-terminal addition of a signal sequence other than that of a mammalian t-PA to mammalian precursor peptide as defined herein is within the scope of the precursor peptide of the invention.**

Patel et al teach construction of a DNA construct encoding a mouse IgSP sequence corresponding to SEQ ID NO:3 operably linked to sequences for export. Patel et al teach that the mouse IgSP is known in the art and predictably can mediate export (see figure 15a).

In KSR International Co. v. Teleflex lnc., 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (Id. At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based

on its precedent that obviousness in part is predicated on use of particular known techniques that are recognized as part of the ordinary capabilities of one skilled in the art. In the instant case, it is accepted that generation of the recited construct is done applying a known sequence to a known method to improve the construct with predictable results. As well, it is within the ordinary skill of the art to use available methodologies to isolate a variety of signal sequences for use in a heterologous sequence and one would have been motivated to do so in order as the ability to modify sequences by applying conventional methodologies. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments

Applicants' arguments have been considered but are not persuasive for the following reasons. One would have been motivated to combine the teachings of Ashkenazi and Patel et al for a variety of reasons. First use of tPA as an export signal directs secretion and export of sequences such that secretion kinetics are improved (see Ashkenazi et al, page 2, line 8-17). Ashkenazi teaches that to this end, a polypeptide to be produced for secretion can be linked to a heterologous signal and/or pro sequence (last sentence page 2). Figure 2D demonstrates that the combination of signal sequence and pro-sequence lead to highly increase levels of secreted protein. Hence, one would look to linking their peptide for secretion to a signal sequence-pro sequence to improve secretion. However, Ashkenazi et al do not teach use of murine IgSP. However, it does not appear that applicants have invented uses of murine immunoglobulin signal

sequence for the secretion of heterologous sequences. In fact, Patel is directed towards use of murine IgSP sequences in recombinant fusion sequences wherein the construct further comprises a secretion sequence. Patel et al do not teach use of tPA pro-peptide sequences. The claimed invention links the two sequences, tPA propeptide and murine IgSP ton one another for the use in secreting proteins. However, the rejection of record sets forth that given the state of the art wherein Ashkenazi teaches linkage of a signal sequence to tPA propeptide to improve protein secretion and Patel et al teach that a known signal sequence is murine IgSP and that this sequence can furthermore function when linked to other regulatory sequences.

When making a rejection under 35 USC 103, TSM is still valid but it is not the only rationale to support a conclusion of obviousness under 35 USC 103 when employing the Graham analysis. For example, **Simple Substitution of One Known Element for Another**. The prior art differs from the claim by the substitution of the signal sequence with that from Patel et al. However, the substituted components were known and the technical ability existed to substitute the components as claimed and the result of the substitution is predictable as demonstrated by the success of Ashkenazi and Patel et al. However, the motivation to combine rests in the establishment by Ashenazi that any heterologous signal sequence can be used wherein Patel et al demonstrate that this sequence functions in a fusion peptide.

For the result to be unexpected, it must be commensurate in scope with the claim. See MPEP §716.02(d) which states, " 6.02(d) [R-2] Unexpected Results Commensurate in Scope With Claimed Invention. Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." "See also In

re Peterson, 315 F.3d 1325, 1329-31, 65 USPQ2d 1379, 1382-85 (Fed. Cir. 2003) (data showing improved alloy strength with the addition of 2% rhenium did not evidence unexpected results for the entire claimed range of about 1-3% rhenium); In re Grasselli, 713 F.2d 731,741,218 USPQ 769, 777 (Fed. Cir. 1983) (Claims were directed to certain catalysts containing an alkali metal. Evidence presented to rebut an obviousness rejection compared catalysts containing sodium with the prior art. The court held this evidence insufficient to rebut the prima facie case because experiments limited to sodium were not commensurate in scope with the claims.).." As demonstrated in figure 2D the combination of signal sequence and pro-sequence lead to highly increase levels of secreted protein and these levels are over that achieved by use of propeptide alone. Hence, the results demonstrated by applicants are not unexpected as the art demonstrates that linkage of a signal sequence to the prepropeptide leads to similar increased levels of secretion.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Primary Examiner
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